that provides modest positive selection for a gut-dwelling strain with the capacity to extract slightly greater energy from a key food source.

It is also possible, however, that the selection pressure could in some cases operate at higher levels (*6*). An individual host's microbiome is not automatically inherited by its offspring. Although gut microbial communities are assembled anew in each individual, preliminary studies suggest that some strains are inherited from parents or siblings and then maintained for years or decades (*7*). Stochastic forces must also shape these microbial communities on an individual level, given that even monozygotic twins share only a limited set of microbial taxa (*8*). However, in the context of microbial sharing through some form of grooming or ingestion of small quantities of feces, the benefit could extend more widely. In a clinical setting, molecular analysis of fecal microbiota transplants between humans has shown that conspecific donor strains are more likely to durably colonize (*9*). Thus, a symbiotic advantage conferred by a microbial strain to an individual might extend to a larger subgroup of the population.

Similarly, across time, if a group of animals are forced to move to a new area and/or eat alternative foods during periodic times of hardship, there may be a selective advantage to retaining "bet-hedging" microbial community diversity across the animal population. Thus, although symbiosis is often experimentally considered as a single microbial strain conferring a singular benefit to a host, with this baseline data, one could also begin to explore evolutionary signatures of symbioses that extend from microbial strains to communities and from individual animals to animal populations.

Moeller *et al.*'s study once again underscores that hominids are multispecies superorganisms. It opens the door to investigations of the genetic features upon which fundamental host-microbiome symbiotic relationships are based. ■

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GENETICS

Demystifying the demise of paternal mitochondrial DNA

A process that eliminates organelle DNA during sexual reproduction is identified

By **Alexander M. van der Bliek**

The vast majority of genes in sexually reproducing eukaryotes can recombine during the production of gametes. This reshuffling generates new genotypes that may provide selective advantages. However, reshuffling does not occur among the few genes in the genomes of cytoplasmic organelles (chloroplasts and mitochondria). Instead, these organelles are almost always transmitted through maternal inheritance (*1*). Why is this phenomenon widespread and how is it achieved? On page 394 of this issue, Zhou *et al.* (*2*) solve part of this puzzle by identifying the enzyme that degrades sperm mitochondrial DNA after fertilization.

"...paternal mitochondria contain a 'self-destruct button' that is activated by fertilization."

Mammalian sperm mitochondria were once depicted as simply being lost, along with the rest of the sperm tail, upon fusion of the sperm's head region with an oocyte during fertilization, but this assumption proved to be wrong. Vertebrate sperm mitochondria are transferred to the oocyte during fertilization, just like paternal mitochondria in other organisms with widely differing sperm structures. In the worm *Caenorhabditis elegans*, for example, the spermatozoids are amoeboid cells that fuse in their entirety with an oocyte during fertilization (see the figure). However, paternal mitochondria, across species, are eliminated during fertilization. Thus, there must be an evolutionarily conserved mechanism that facilitates this removal.

The story gained momentum with the realization that organelles, such as mitochondria, can be selectively destroyed by autophagy. In this complex cellular process, cytoplasmic components, including entire organelles, are encapsulated by a so-called "isolation membrane," followed by fusion with lysosomes and wholesale degradation by lysosomal proteases and lipases (*3*). The removal of mitochondria by autophagy (called "mitophagy") can be restricted to an individual mitochondrion that shows a loss of membrane potential. It can also be used more globally to remove all mitochondria from a cell—for example, during maturation of mammalian red blood cells. *C. elegans* paternal mitochondria are removed by mitophagy quickly after fertilization (*4, 5*). A common autophagy adapter protein called light chain 3 (LC3) (LGG-1 in *C. elegans*) accumulates on paternal mitochondria, consistent with degradation through a canonical autophagy pathway. Paternal mitochondria are presumably marked in some way for degradation, distinguishing them from maternal mitochondria. *Drosophila* sperm degrade most of their mitochondrial DNA prior to fertilization (*6*), but *Drosophila* and mouse embryos also show selective mitophagy of paternal mitochondria after fertilization, consistent with a common mechanism for maternal inheritance (*5, 7*).

Initial triggers for degrading the paternal mitochondria are unknown. Zhou *et al.* helped address this question by showing that paternal mitochondria quickly lose inner membrane integrity after fertilization. Surprisingly, mitochondrial endonuclease G (ENDOG), encoded by the *CED-3 protease suppressor-6* (*cps-6*) gene in *C. elegans,* is required for rapid degradation of paternal mitochondrial DNA after fertilization. The *Drosophila* homolog of CPS-6/ENDOG acts during sperm maturation (*6*), but in *C. elegans*, this protein acts before autophagosomes fuse with lysosomes, as mutations in *cps-6* lead to an accumulation of autophagy intermediates in the embryo.

Several conclusions can be drawn from these data. One is that internal breakdown precedes autophagy, which implies that paternal mitochondria contain a "self-destruct button" that is activated by fertilization. Simply tagging paternal mito-

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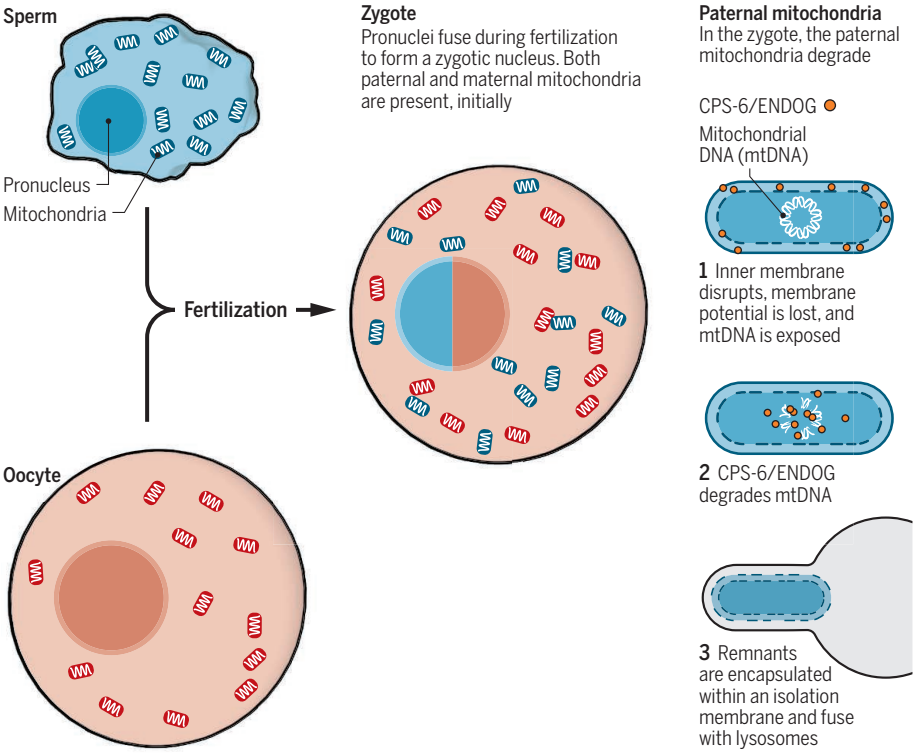
Self-destruct button?

Paternal mitochondrial DNA, across species, is eliminated during fertilization, as illustrated below for the worm *C. elegans*. A model for the underlying mechanism involves disruption of paternal mitochondrial membranes.



chondria with degradation markers, such as ubiquitin, is not enough to explain this mystery. Some unique feature of paternal mitochondria might actively disrupt their inner membranes when these organelles are exposed to oocyte cytoplasm. Another conclusion is that degradation of mitochondrial DNA by CPS-6/ENDOG accelerates mitochondria destruction by autophagy, even though their inner membranes are already disrupted and lysosomes have their own endonucleases. The extra precautions to degrade paternal mitochondrial DNA suggest that this step is critical for embryogenesis. Indeed, Zhou *et al.* show that deletions in *cps-6* slow cell division during embryogenesis and cause embryonic lethality in crosses with strains containing heterologous mitochondrial DNA. These results highlight the importance of eliminating paternal mitochondrial DNA.

CPS-6/ENDOG was first identified as a critical factor for programmed cell death (apoptosis) (*8*). It normally resides in the mitochondrial intermembrane space, but is released into the cytosol during apoptosis to degrade nuclear DNA. Likewise, cytochrome c is an integral part of the mitochondrial electron transport chain, but is released from the mitochondrial intermembrane space during apoptosis to activate caspases (*9*). Other apoptosis factors that are released from the mitochondrial intermembrane space during apoptosis, such as apoptosis-inducing factor–1 (AIF-1), most likely also have a normal housekeeping function. CPS-6/ENDOG thus joins a growing list of dual-function mitochondrial proteins with a role in normal growth and development as well as in apoptosis.

A model arising from the findings of Zhou *et al.* is that soon after fertilization, morphological disruptions of paternal mitochondrial membranes occur. This presumably exposes mitochondrial DNA to the CPS-6/ENDOG endonuclease in the intermembrane space. The authors also observed concomitant loss of mitochondrial membrane potential, consistent with holes in the mitochondrial inner membrane. Loss of membrane potential activates the mitophagy machinery, so how paternal mitochondrial inner membranes are disrupted becomes of paramount importance. Conversely, it is unclear whether CPS-6/ENDOG affects mitophagy in other developmental stages or cell types, and whether it also functions when restricted to the mitochondrial intermembrane space. Could it, for example, be a guardian against mitochondrial DNA that might inadvertently escape from the mitochondrial matrix through occasional breaches in the mitochondrial membranes?

Maternal inheritance has a broader societal impact than one might expect from the small number of genes encoded by mitochondria and chloroplasts. Subtle mutations in human mitochondrial DNA can provide selective advantages, such as cold tolerance, suggested by tracing extensive lineages of human migration with mitochondrial DNA (*1*). These seemingly innocuous changes in mitochondrial DNA can alter nuclear gene expression through cross-talk between genomes in the nucleus and mitochondria (*10*). Such interaction could explain the incompatibility with paternal mitochondria that was observed by Zhou *et al.* in genetic crosses with *C. elegans cps-6* mutants.

An awareness of the interplay between mitochondrial and nuclear genes might influence our understanding of mutations in mitochondrial DNA that cause debilitating diseases, including those that affect optic nerves, muscles, and metabolism (*1*). U.S. and UK science and ethics panels gave limited approval to preventing these diseases by in vitro fertilization with nuclear transfer using genetic material from three parents: sperm from the father, an oocyte nucleus from the mother, and oocyte cytoplasm from a second female with healthy mitochondrial DNA. Recent experiments to test the effectiveness of this approach have, however, uncovered difficulties with heteroplasmy (heterogeneous population of mitochondrial DNA) (*11*). Small amounts of residual mutant mitochondrial DNA sometimes compromise the larger population of healthy mitochondrial DNA through genetic drift (*12*). Further mechanistic studies of mitochondrial inheritance may help solve this problem. ■

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